EDITORIALS

MYOCARDIAL METABOLISM IN DIABETES

Early studies on cardiac metabolism in diabetes have dealt with investigations on the isolated heart or the heart-lung preparation. Later the studies were extended to intermediary metabolism using tissue slices or homogenates. Already during the early phase of these investigations it was discovered that the diabetic heart in vitro had not lost its ability to use sugar. Using the hearts of depancreatized dogs in situ, a positive myocardial glucose balance was found. Later, tissue slices from hearts of diabetic dogs were found to utilize pyruvate and lactate less readily than slices from normal animals. Similarly, diminished utilization of C^{14}-labeled pyruvate was observed in both cardiac and diaphragmatic muscle of diabetic animals and the fraction of pyruvate converted to carbon dioxide was decreased. The addition of insulin had no influence on the conversion of labeled pyruvate to $C^{14}O_2$ in cardiac muscle in vitro. The metabolic deficiency was found to extend also to utilization of fatty acids. This appeared to be related to the disturbance in carbohydrate metabolism, since the transfer of energy required for fatty acid synthesis seemed to be derived mainly from coupled reactions involving the simultaneous oxidation of some carbohydrate intermediate. Thus, in general, the diabetic state appeared to be accompanied by a marked decrease in the ability to synthesize fatty acids from glucose, lactate or pyruvate.

In experiments on the whole animal, deficient protein synthesis in diabetes was also found, since high fasting plasma amino acid levels were frequently present in patients with severe untreated diabetes. It appeared, therefore, that utilization of carbohydrates by the diabetic organism is diminished and that the diabetic organism is also deficient in utilization of fat and protein. Whether this is the result of disturbances in glucose transfer across membranes; or of interferences with the hexokinase reaction; or of oxidative phosphorylation; or of oxidative reactions within the Krebs cycle remains undetermined.

Coronary sinus catherization has made it possible to investigate over-all metabolic changes of the diabetic heart in patients with diabetes mellitus and in dogs made diabetic with alloxan. This type of investigation bears a close similarity to earlier methods of study, such as the isolated heart or the heart-lung preparation. This technic has its limitations. For example, one can only determine the balance of foodstuffs across the heart, and conclusions on the fate of these substrates in the cell, the participation of enzyme systems or the localization of metabolic defects, are not possible. However, these balance studies are carried out on the heart beating in its natural environment.

The results obtained on the diabetic heart of humans and dogs with this technic have shown that myocardial usage of carbohydrates is reduced and that utilization of noncarbohydrate material is increased. Apparently the heart in situ is not exempt from the most important metabolic defect in diabetes, that of deficient utilization of carbohydrate. The decreased ability of the diabetic human and dog's heart to utilize lactate is particularly conspicuous. The marked reduction of myocardial usage of lactate is primarily responsible for the reduction in the total amount of energy available from the carbohydrate fraction. This agrees with data obtained on the intact diabetic animal. For instance, the arterial lactate concentration of depancreatized dogs reaches higher values during exercise than in the nondiabetic animal. Pyruvate extraction by the diabetic human and dog's heart is within normal limits. However, when one considers that the normal pyruvate extraction occurs in the presence of a significant elevation in arterial concentration of pyruvate, this finding suggests diminished usage of pyruvate. It had been previously shown that tissue slices from diabetic dogs utilize pyruvate and lactate less readily than those from normal animals. Furthermore, the rate of oxidation of acetate and pyruvate to carbon dioxide was found to be diminished in diaphragms from alloxan diabetic rats.

In the face of reduced carbohydrate utilization, a relatively large amount of noncarbohydrate material must be used by the heart for energy production. This is actually the case since the human heart in patients with diabetes mellitus extracts a significantly greater amount of fatty acids than does the nondiabetic heart. Fatty acids may be stored by the diabetic heart since the oxygen extraction ratio of fatty acids which represents their contribution to the total myocardial oxygen extraction, is above 100 per cent. The usage of ketone bodies by the diabetic heart is also increased.

If, under those conditions, insulin is to correct the metabolic defects found in the diabetic heart, it should result in a relative increase in myocardial utilization of fatty acids and ketones. The hormone results in a significant fall in blood sugar, but this occurs without changes in myocardial usage and extraction of glucose. This implies that insulin causes a relative increase in myocardial glucose utilization. After insulin injections into diabetic dogs, the concentration of pyruvate in coronary vein blood frequently exceeds that in arterial blood. This diminished myocardial uptake of pyruvate by the heart muscle may be an indication of increased catabolism of endogenous carbohydrate in heart muscle, initiated by a rapidly falling blood sugar level in these severely diabetic organisms. This may be due to a block between pyruvate and the Krebs cycle resulting from a reduced thiamine content of heart muscle. However, the condensation of pyruvic acid with oxalacetic acid is so complex that it is impossible to speculate on the exact location of this defect. Equally surprising was the finding that insulin failed to correct the metabolic defect responsible for diminished myocardial lactate usage. Arterial lactate concentration rose, but myocardial extraction of lactate hardly changed. Insulin resulted in a fall in the blood concentration in fatty acids without significantly affecting their myocardial usage or extraction. It appeared likely that the fall in blood concentration of fatty acids was due to a decreased mobilization from fat deposits.

The results obtained on the diabetic heart in situ demonstrate a great variety of metabolic defects. The diabetic heart is deficient in glucose, pyruvate and lactate utilization. In addition, the defect extends to the metabolism of protein and fat. It is unlikely, however, that these diffuse changes in energy production result in disturbances in energy utilization of the heart. The fundamental importance of diabetes in cardiology does not rest on primary metabolic disease of heart muscle but rather on the frequency with which diabetes results in coronary vascular changes and its complications.

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SCIENTIFIC PROGRAMS OF AFFILIATE ASSOCIATIONS

The editors of DIABETES desire to call the attention of members of the Affiliate Associations of the American Diabetes Association to the desirability of using the *Journal* as a vehicle for announcing scientific programs of the Affiliates.

Recent experience of the New York Diabetes Association in which more than 900 persons from twenty-two states attended the Fourth Annual Symposium of this